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10/530,108	04/01/2005	Silvia Trasciatti	NOTAR4.001APC	2649

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EXAMINER
JUEDES, AMY E

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,108	TRASCIATTI ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,10-15,17,18 and 25-28* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-8, 10-15, 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 4/11/08, are acknowledged.

Claims 2-4, 9, 16, and 19-24 have been cancelled.
Claims 1, 5-8, 10-13, 15, and 17-18 have been amended.
Claims 25-28 have been added.
Claims 1, 5-8, 10-15, 17-18, and 25-28 are pending.

2. Claims 17-18 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1, 5-8, 10-15, and 25-28 are being acted upon.

3. The rejection of the claims under 35 U.S.C. 112 second paragraph as outlined in sections B)-L) of the previous office action is withdrawn in view of Applicant's amendment to the claims.

4. The rejection of the claims under 35 U.S.C. 103 is withdrawn in view of Applicant's amendment to the claims. The cited references do not teach adding an inoculum in an initial volume of 1/10 to 1/6 of the multi-chamber stack final volume.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-8, and 10-15 stand rejected, and claims 25-28 are rejected, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth previously, A) Claim 1 is drawn to a method of expansion of TALL lymphocytes, but the only recited step is growing cells in a single fermentation unit. It is unclear how growing any generic "cell" could result in the expansion of TALL lymphocytes (i.e. the claims do not require that TALL lymphocytes be grown). The claims don't even require growing lymphocytes.

Applicant's arguments filed 4/11/08 have been fully considered, but they are not persuasive.

Applicant argues that the claims specify a process for amplifying TALL-104 cells by inoculating with TALL-104 cells.

The claims are drawn to a process for amplifying TALL-104 lymphocytes comprising inoculating a multi-chamber stack with any “cell”. As noted above, it is unclear how inoculating any generic "cell" could result in the expansion or amplification of TALL-104 lymphocytes.

6. Claims 13-14 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

As set forth previously, The claims are incomplete for omitting essential steps. While all of the technical details need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. In the instant case, the claims are drawn to a process for the preparation of frozen bags of TALL lymphocytes, however, the only recited method step is growing said lymphocytes in homogenous conditions in a single fermentation unit. Thus, it is unclear how the method could result in the production of a frozen bag of lymphocytes.

Applicant’s arguments filed 4/11/08 have been fully considered, but they are not persuasive.

Applicant argues that the amendment to the claims obviates the rejection.

However, the claims are still drawn to a method for preparing frozen bags of TALL lymphocytes using the process of claim 1. Claim 1 is drawn to a process for amplifying TALL-104 lymphocytes in a multi-chamber stack and recovering said lymphocytes. Thus, it is unclear how said method could result in the production of frozen bags of lymphocytes without any other steps (i.e. collecting the cells into a bag, for example).

7. The following are new grounds of rejection necessitated by Applicant's amendment.

8. Claims 1, 5-8, 10-15, and 25-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite in the recitation of adding an inoculum of cells in an initial volume of “1/10 to 1/6 of the

muti-chamber stack final volume" and further adding a volume of complete medium "corresponding to that contained in the multi-chamber stack". As an initial matter, it is noted that the claim recites "muti" chamber instead of "multi" chamber in line 4. Furthermore, it is not clear what initial volume or corresponding volume is to be added. For example, the initial inoculum might represent 1/10 of the total volume capacity of the chamber, or it might represent 1/10 of the final volume added to the chamber after the amplification step. Said volumes might be entirely different. For example, if the chamber has a capacity of 1L, 1/10 of the final volume capacity would be 100 mls. However, if the total culture volume after the amplification step is less than the capacity of the chamber (for example, 300 mls), an inoculum of 1/10 of the final volume would only be 30mls. Additionally, the claims recite that the second volume of complete medium should "correspond" to that contained in the multi-chamber stack. Said medium might be a similar type of medium or a similar volume of medium (i.e. corresponding to the medium or the volume of medium).

B) Claim 27 recites the limitation "the bag" in line 1. There is insufficient antecedent basis for this limitation in the claim, or in claims 1, 10, or 26.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-8, 10-15, and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method comprising adding an inoculum in an initial volume of "1/10 to 1/6 of the multi-chamber stack final volume"

(Claim 1 dependent claims 5-8, 10-15, and 25-28).

B) A method comprising amplifying the cell number by "adding a volume of complete medium corresponding that that contained in the multi-chamber stack" (Claim 1 dependent claims 5-8, 10-15, and 25-28).

C) A method wherein the cellular density of the inoculum is "at least 0.75 x 10^6 cells/ml" (Claim 6).

Applicant indicates that support for the new limitations can be found on pages 6-7 of the specification. A review of the specification fails to reveal support for the new limitation.

Regarding A), the instant specification discloses on page 6 that cells can be added in an inoculum in a volume ranging from 1/6 to 1/10 of the cell factory "final volume capacity". However, the instant claims recite a volume of 1/6 to 1/10 of the multi-chamber stack "final volume" which has a broader scope than what is disclosed by the specification. While the "final volume" of the claims might encompass the "final volume capacity" of the chamber, it might also encompass inoculating any volume that is 1/6 to 1/10 of the total final volume of culture medium added after the amplification step. For example, the claims might encompass inoculating in a 10 ml volume, followed by adding 90 mls of medium in the amplification step. In this case, the 10 mls would be 1/10 of the final volume of medium in to the cell factory. However, 10mls would be well below 1/10 of the "final volume capacity" of a cell factory, as disclosed by the specification.

Regarding B), the instant specification on page 7 discloses that a volume of complete medium corresponding to that contained in the cell-factory is added every 3-5 days. However, the claims have a much broader scope and encompass adding a volume of corresponding medium at any time (i.e. 1 day, 2 hours, 10 days, etc.).

Regarding C), the specification discloses on page 7 that the inoculum is preferably 0.75 x 10^6 cells per ml. However, the disclosure of a single cell concentration is not adequate to support the range of "at least" 0.75 x 10^6 cells, as claimed.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 5-8, 10-13, 15, 25-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/26284, in view of Gambacorit-Passerini et al. (of record) and Tuyaerts et al. (of record), as evidenced by the product information for Nunc cell factories.

WO 94/26284 teaches that TALL-104 lymphocytes are an immortal killer cell line that permanently and rapidly grow in the presence of IL-2 in vitro (see page 19, in particular). WO 94/26284 further teaches a process for amplifying TALL-104 lymphocytes comprising growing the cells in the presence of IMDM medium supplemented with 10% fetal bovine serum and IL-2 (i.e. an antibiotic free medium). WO 94/26284 further teaches adding fresh medium containing IL-2 on a biweekly basis, which results in the continuous growth of TALL-104 cells in a exponential fashion (i.e. adding a volume of medium “corresponding” to the initial IL-2 containing medium to amplify the cells, see page 24 and 26 in particular). WO 94/26284 also teaches growing the TALL-104 cells with 100 U/ml of IL-2 (see page 24 in particular). WO 94/26284 also teaches using TALL-104 cells that have been modified by gamma irradiation, which results in loss of ability to synthesize DNA and RNA (i.e. “genetically” modified TALL-104 cells, see page 22 in particular). WO 94/26284

also teaches that the TALL-104 lymphocytes can be used for adoptive transfer therapy in humans (see page 18 and 38 in particular).

WO 94/26284 does not teach amplifying the cells in a 10 chamber stack, freezing the cells, or a medium comprising human serum.

Gambacorti-Passerini et al. teach a method for the large scale production of lymphocyte killer cells comprising culturing the cells at a concentration of 1.5 x 10^6 cells/ml in a 10 floor multi-chamber stack (Nunc Cell Factories™, see page 524 in particular). Gambacorti-Passerini et al. also teach that the killer lymphocytes can be grown in range of concentrations (2.5%, 5% or 10%) of homologous human serum without affecting cell recovery (see page 525 in particular). Gambacorti-Passerini et al. also teach harvesting the lymphocytes into bags, and freezing the bags (see page 524-525 in particular). Gambacorti-Passerini et al. also teach that the large scale production of the killer cells in the multi-chamber stacks results in fully comparable activation and function of the cells compared to cells grown in standard flasks (see page 527 in particular). Gambacorti-Passerini et al. also teach that the culture method using the multi-chamber stacks is faster and more affordable than other cell culture methods (see page 529 in particular).

Tuyaerts et al. teach that cytokine dependent cells can be grown in multi chamber stacks (Nunc Cell Factories™) by adding the cells in an initial volume of 160 mls of cytokine containing medium per chamber, followed by supplementing the cells with complete medium containing cytokines every 48 hours after the initiation of the culture (i.e. a volume of medium "corresponding" to the medium in the multi-chamber stack, see page 138 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to grow the TALL-104 cells of WO 94/26284 using a multi-chamber stack, as taught by Gambocorti-Passerini et al. and Tuyaerts et al. The ordinary artisan would be motivated to grow the TALL-104 cells in a multi chamber stack, since Gambacorti-Passerini et al. teach that it is faster and more affordable than other cell culture methods. Furthermore, it would have been obvious to add the TALL-104 cells to the multi-chamber stack in a volume

as of 160 mls/chamber, as taught by Tuyaerts et al., followed by adding a "corresponding" medium with IL-2 on a biweekly basis, as taught by WO 94/26284. The ordinary artisan would be motivated to add the fresh medium comprising IL-2, since WO 94/26284 teaches that addition of said medium results in the continuous and exponential growth of TALL-104 lymphocytes. Additionally, the ordinary artisan would have a reasonable expectation of success in growing the TALL-104 lymphocytes in a multi-chamber stack, since Gambocorti-Passerini et al. teach that killer lymphocytes can be grown in said chambers, and Tuyaerts et al. teach that said chambers are amendable to addition of fresh medium containing cytokines. Furthermore, it would have been obvious to add the cells at a density of 1.5 x 10^6 cells, since Gambacorti-Passerini et al. teach that such a concentration is suitable for growing killer lymphocytes in a multi chamber stack. Additionally, the ordinary artisan would have had a reasonable expectation of success in amplifying the TALL-104 lymphocytes to obtain at least 1 x 10^9 cells, since WO 94/26284 teaches that TALL-104 lymphocytes expand exponentially when grown in IL-2. Furthermore, as evidenced by the Nunc product information for a multi-chamber stack, a 10 chamber stack is 335mm x 205mm x 190 mm (i.e. has a final volume capacity of ~13 L). Therefore, adding the inoculum at 160mls/chamber, or a total of 1.6 L for 10 chambers, as made obvious by WO 94/26284, Gambocorti-Passerini et al., and Tuyaerts et al., would correspond to ~1/8 of the total final volume capacity of the chamber. Moreover, the ordinary artisan would have been motivated, and have a reasonable expectation of success in substituting the homologous human serum taught by Gambacorti-Passerini et al. for the fetal bovine serum taught by WO 94/26284 et al., since the cells of WO 94/26284 et al. are used for human therapy, and homologous serum would be expected to be to avoid any potential for an adverse response to foreign bovine proteins in human patients. Additionally, it would have been obvious to perform a pre-expansion of the TALL-104 killer cell lines taught by WO 94/26284 to obtain the appropriate number of cells for inoculating the multi-chamber stack. Additionally, it would have been obvious to freeze the TALL-104 lymphocytes to provide a convenient and ready to use population of cells, and the ordinary artisan would have had a reasonable expectation of success, since Gambacorti-Passerini et al. teach that killer lymphocytes can be harvested from a multi chamber into bags and frozen.

12. Claims 14 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/26284, Gambacorti-Passerini et al., and Tuyaerts et al., as applied to claims 1, 5-8, 10-13, 15, 25-26 and 28 above, and further in view of U.S. Patent 6,491,678.

The combined teachings of WO 94/26284, Gambacorti-Passerini et al., and Tuyaerts et al. are discussed above.

They do not teach creating a sampling chamber in the frozen bags for the purpose of performing quality controls.

The '678 patent teaches a freezing bag that can be sealed to create sample chamber that can be detached without thawing for testing the suitability of the frozen cells (see column 3 in particular). The '678 patent teaches that the sample chamber can comprise up to 1 ml (see column 9 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to create a detachable sample chamber comprising up to 1 ml, as taught by the '678 patent, in the method of freezing the killer cells in bags, made obvious by WO 94/26284, Gambacorti-Passerini et al., and Tuyaerts et al. The ordinary artisan would have been motivated to do so, since the '678 patent teaches the detachable chamber can be used to test the suitability of frozen cells without having to thaw the frozen bag.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 6am - 2pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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